01-12-09 1654

PTO/SB/21 (11-08)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/522,911
Filing Date	July 7, 2005
First Named Inventor	Senter, Peter D.
Art Unit	1654
Examiner Name	Christina Bradley
Attorney Docket Number	018891-004310US

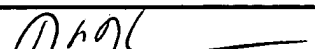
Total Number of Pages in This Submission .

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Response to Examiner's Requirement for Information
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please identify below):
  1. Slides by Brian E. Toki, et al.
  2. Return Postcard

Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

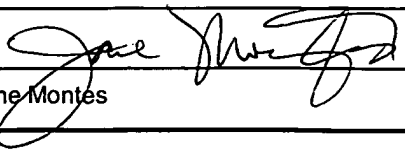
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Townsend and Townsend and Crew LLP		
Signature			
Printed name	Mark H. Hopkins, Ph.D.		
Date	January 8, 2008	Reg. No.	44,775

CERTIFICATE OF TRANSMISSION/MAILING

Express Mail Label: EV 325547419 US

I hereby certify that this correspondence is being deposited with the United States Postal Service with "Express Mail Post Office to Address" service under 37 CFR 1.10 addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature			
Typed or printed name	Jane Montes	Date	January 8, 2008

v

PATENT
Attorney Docket No.: 018891-004310US
Client Ref. No.: 1000-00212US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 7034
Peter D. Senter et al.	Examiner: Christina Bradley
Application No.: 10/522,911	Technology Center/Art Unit: 1654
Filed: July 7, 2005	RESPONSE TO EXAMINER'S REQUIREMENT FOR INFORMATION UNDER 37 C.F.R. §1.105
For: DRUG CONJUGATES AND THEIR USE FOR TREATING CANCER, AN AUTOIMMUNE DISEASE OR AN INFECTIOUS DISEASE	
Customer No.: 51535	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Requirement for Information mailed December 17, 2008, please enter the following remarks:

REMARKS/ARGUMENTS

In response to the Requirement for Information, Applicants submit what they presently believe to be a complete copy of the slides accompanying the oral presentation of Toki *et al.* at the 223rd ACS National Meeting in Orlando, FL on April 7-11 titled "Cures and regressions of established tumor xenografts with monoclonal antibody auristatin" given by Brian Toki. A copy of the abstract corresponding to this oral presentation (CAS 2002:190266) was cited as item C12 in the Information Disclosure Statement filed on July 7 2005. Applicants request that the full presentation become of record in a PTO-892 in this matter.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Mark H. Hopkins, Ph.D.
Reg. No. 44,775

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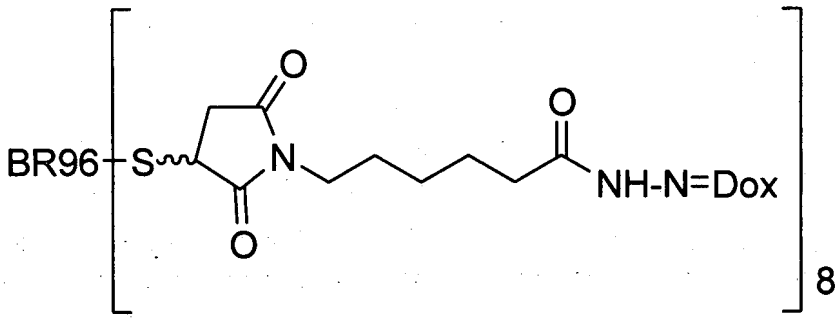
Attachments
M3H:jcm
61757556 v1

Cures and regressions of established tumor xenografts with monoclonal antibody auristatin E

Brian E. Toki

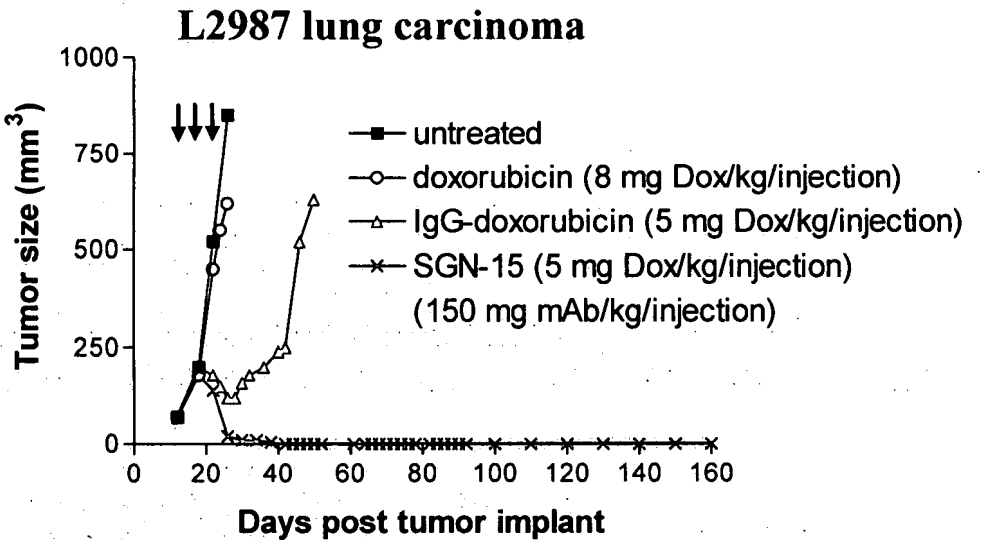
Antibody Drug Conjugates

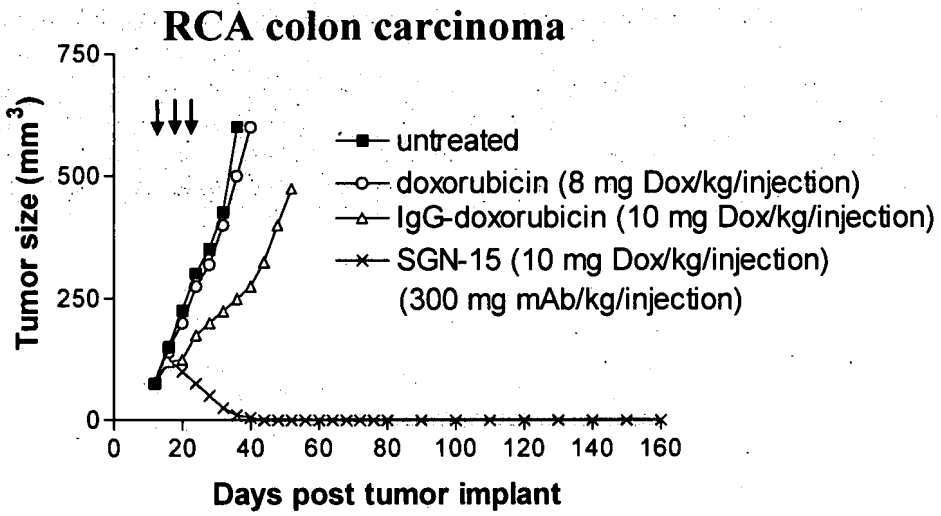


- **Doxorubicin is attached to reduced BR96 through a hydrazone linker (SGN-15).**
- **After binding to tumor antigens, the conjugate is very rapidly internalized into acidic vesicles.**
- **Native doxorubicin is released ($t_{1/2}$ 190 minutes at pH 5, 130 minutes in lysosomes).**

Willner D., et al. *Bioconjugate Chem.* **1993**, *4*, 521

Preclinical Antitumor Efficacy of SGN-15

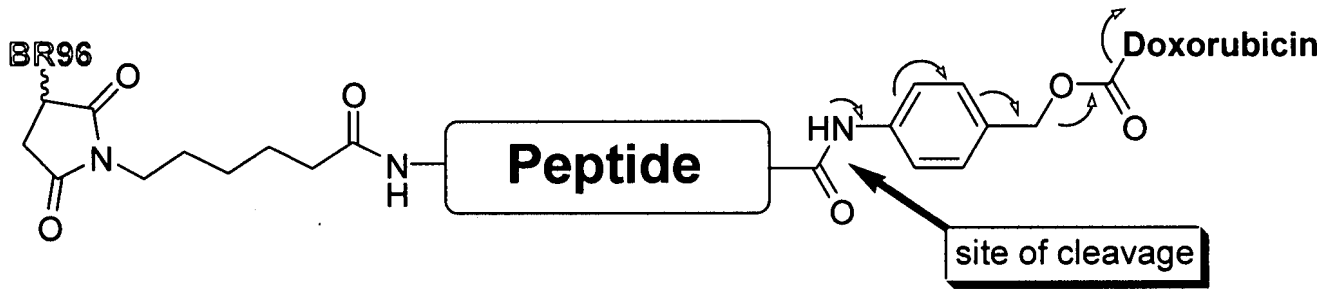




Considerations for Improved Therapeutic Efficacy

- Internalizing mAbs with high tumor selectivity
- Optimized linker technology

Peptide Linked Doxorubicin Conjugates



After extensive analysis, Val-Cit and Phe-Lys were found to have the most promising characteristics.

Half Lives

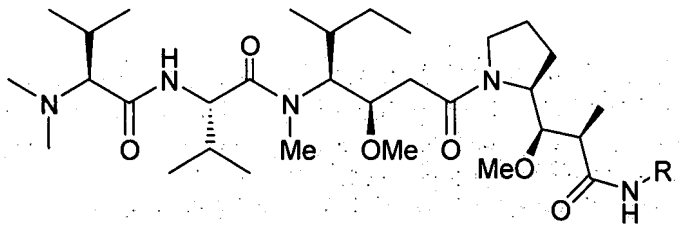
Conjugate	Human Plasma	Lysosomal Preparations
Phe-Lys	>20 days	55 min
Val-Cit	>16 days	159 min

Dubowchik, G.M.; Walker, M.A. *Pharmacology & Therapeutics*, **1999**, 67

Considerations for Improved Therapeutic Efficacy

- Internalizing mAbs with tumor selectivity
- Optimized linker technology
- Potent drugs

Potent Drugs for Immunoconjugates: the Dolastatins and Auristatins



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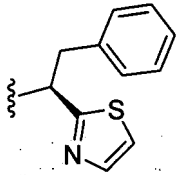
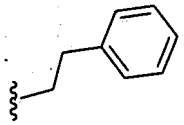
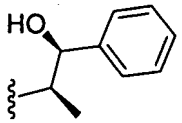


dolastatin 10 (phases 1,2 - BASF)



Auristatin PE (phase 1- Teikohu)



Auristatin E (Seattle Genetics)

Pettit, G.R. *The Dolastatins*; Progress in the Chemistry of Organic Natural Products, No. 70. Wien-New York: Springer-Verlag. 1997.

Compound	Cell Line	IC_{50}
Doxorubicin	LX-1 (lung)	1 μ M
	L2987 (lung)	5 μ M
	MCF-7 (breast)	8 μ M
Auristatin E	LX-1 (lung)	8 nM
	L2987 (lung)	2 nM
	MCF-7 (breast)	2 nM

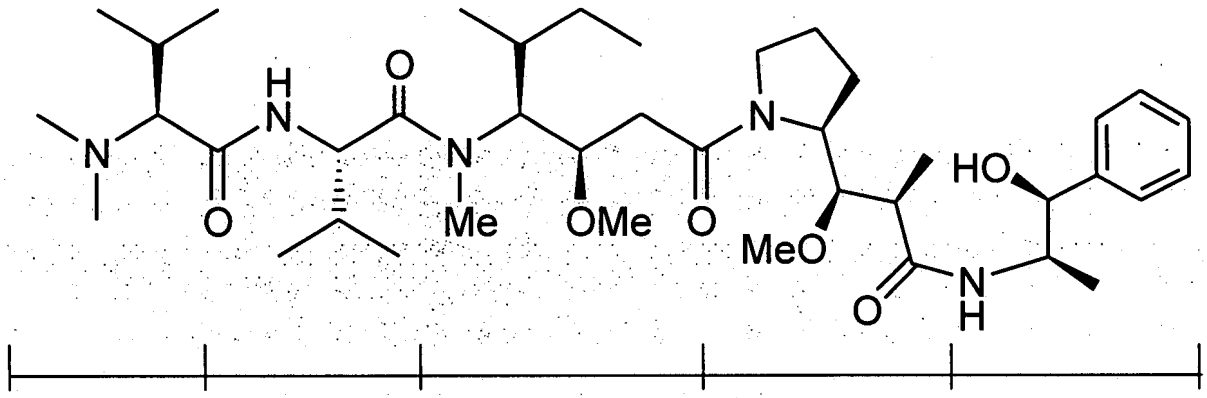
Dolastatin 10 is a natural product from the Indian Ocean sea hare, Dolabella auricularia. The auristatins are totally synthetic.

Auristatin E

- **Mechanism of action:** metaphase arrest through inhibition of tubulin polymerization.
- **Potency:** 3 orders of magnitude greater than doxorubicin.
- **Stability:** stable in serum and in lysosomal preparations.
- **Conjugation:** through the norephedrine hydroxyl group and other functionalities introduced by chemical modification of AE or total synthesis.

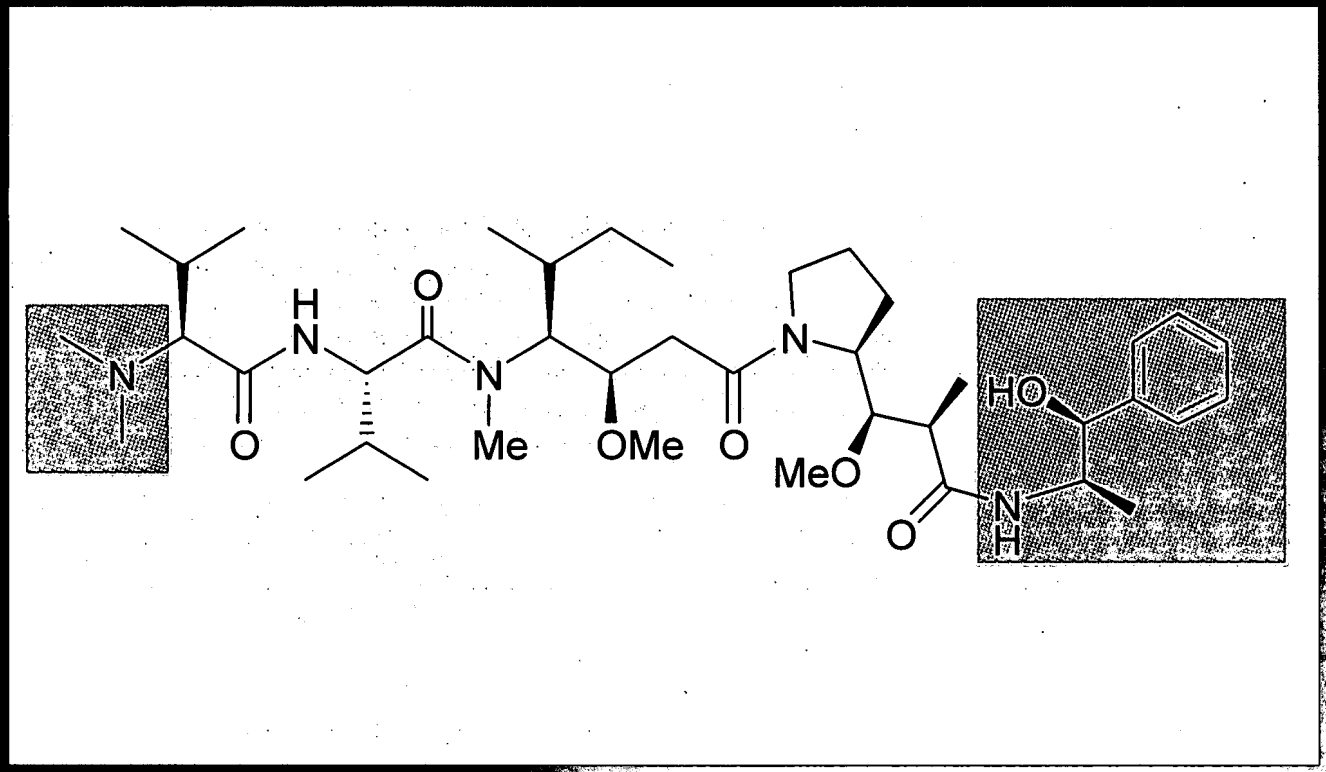
Supply of Auristatin E

- Multigram quantities available through total synthesis
- Synthesis is convergent, scaleable



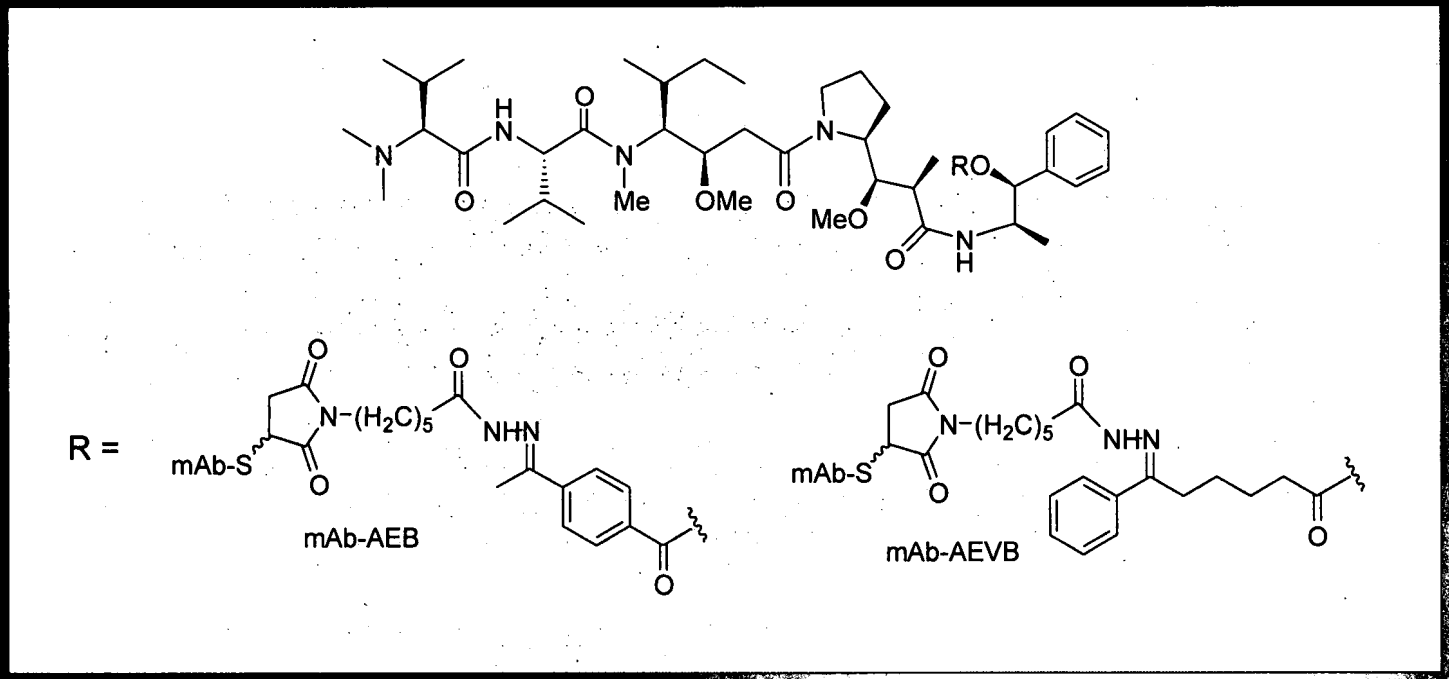
Pettit, et al. *Anticancer Drug Design*, **1998**, *13*, 243

Synthetic Auristatin Analogues



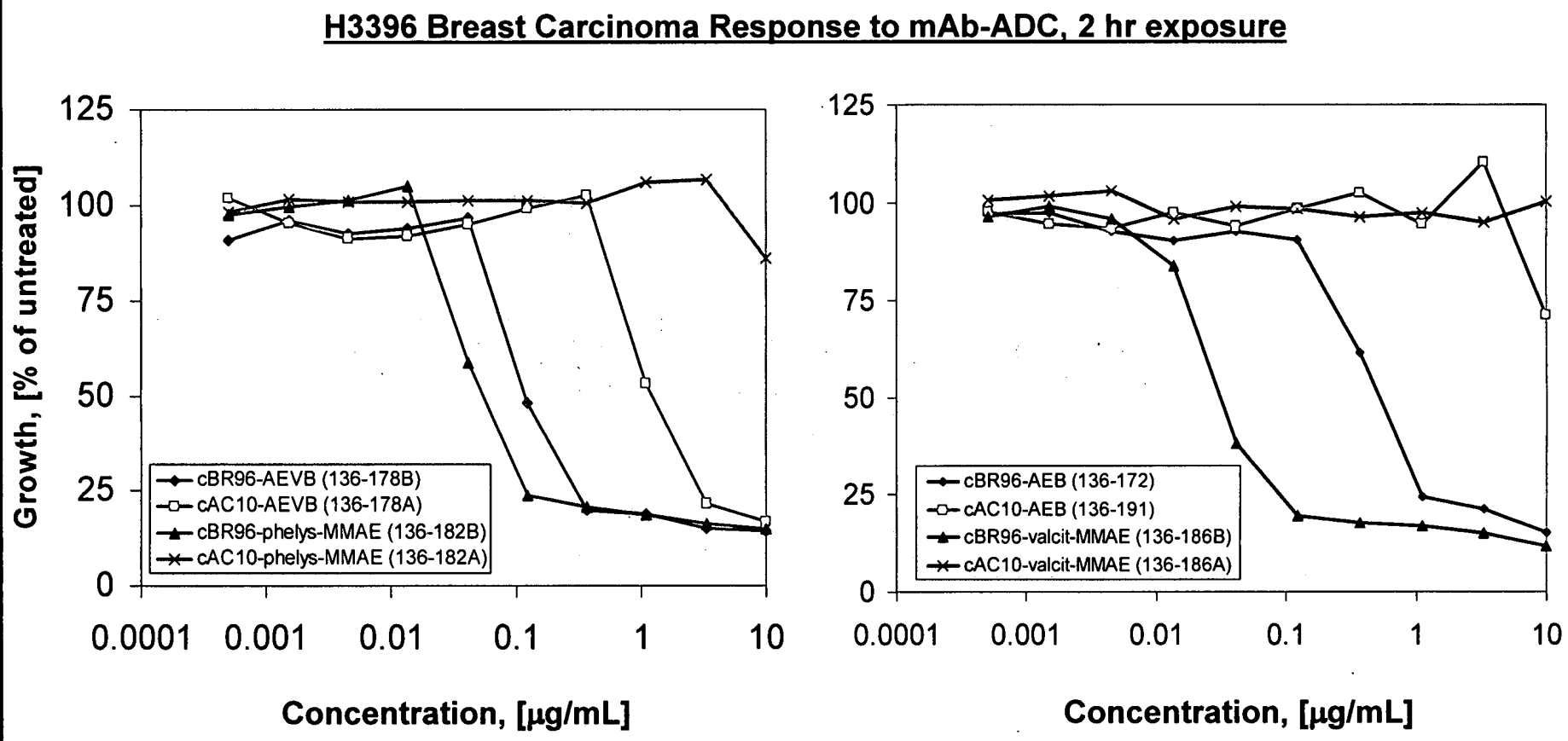
- Analogues designed for enhanced activities
- Provide new sites and chemistries for mAb attachment

Auristatin E Conjugates: Benzylhydrazone Esters



- AEB - $t_{1/2}$ pH 5.0 = 8 h, pH 7.2 > 110 h, human serum = 277 h
- AEVB - $t_{1/2}$ pH 5.0 = 3 h, pH 7.2 > 60 h

Auristatin E Conjugates: *In Vitro* Specificity

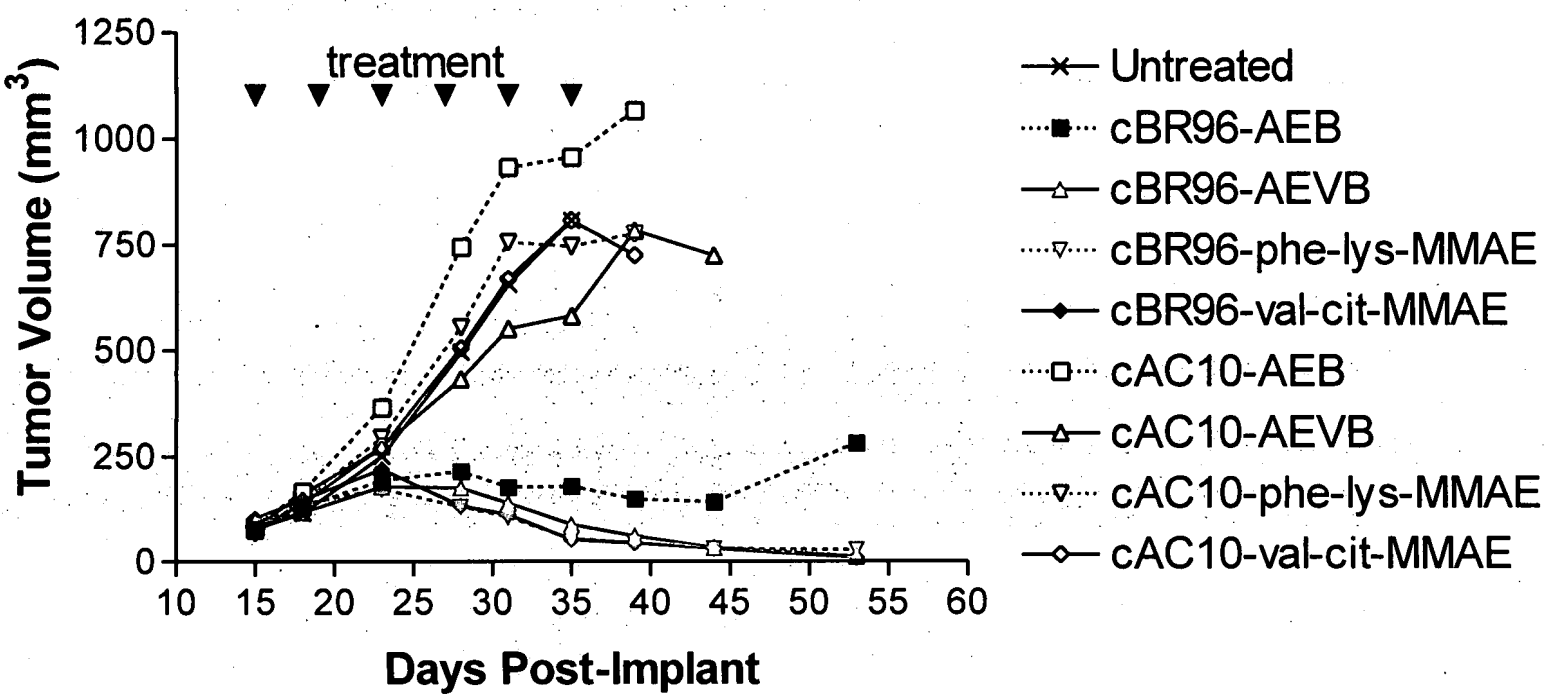


- Improved specificity with peptide conjugates

In Vivo Therapeutic Efficacy

L2987 Human Lung Adenocarcinoma

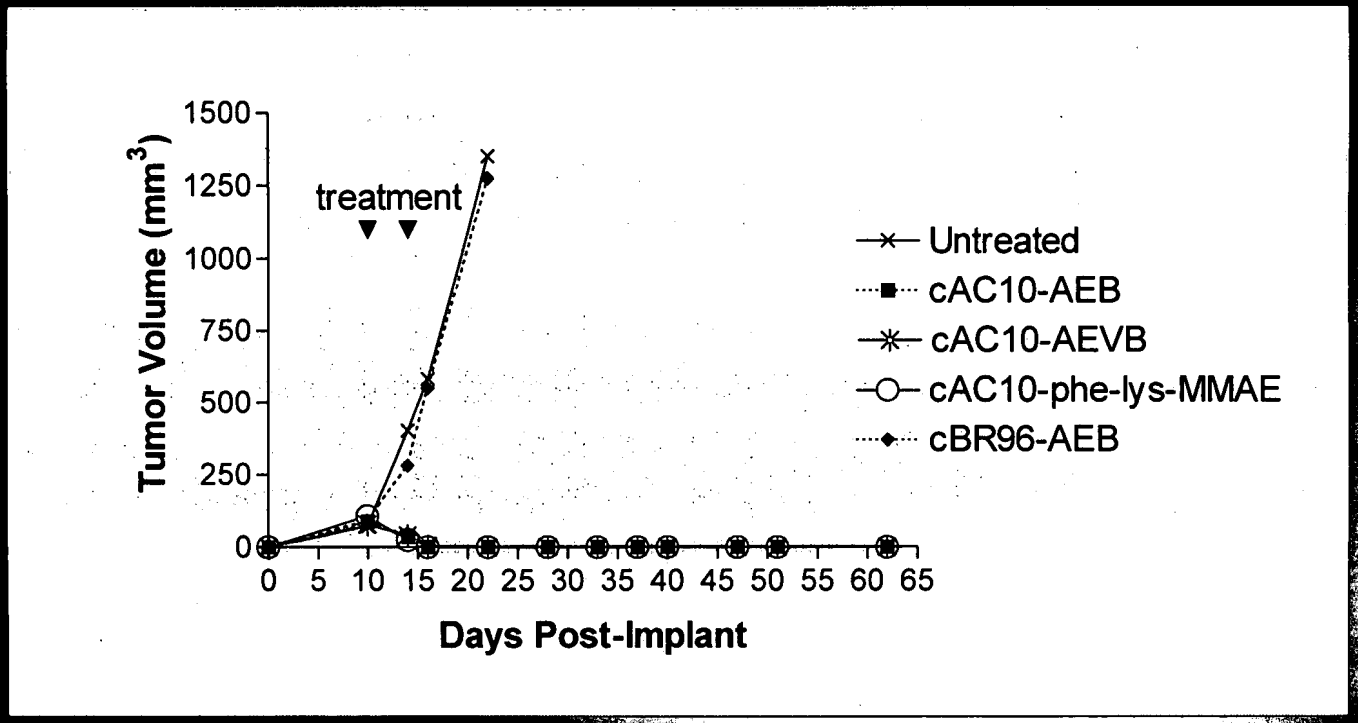
3 mg/kg/injection



In Vivo Therapeutic Efficacy

Karpas ALCL Tumors

1 mg/kg/injection



- Significant efficacy at 1 mg/kg/injection
- Selective activity at < 1/30th the MTD

Antibody Drug Conjugates

- Auristatin E analogues are potent cytotoxic agents that inhibit microtubule polymerization
- Both hydrazone and peptide linker conjugates have proven to be stable in serum and have shown effective tumoral release of drug
- The peptide conjugates show higher specificity than the hydrazone conjugates *in vitro*
- Auristatin conjugates such as AEVB and MMAE show efficacy at doses as low as 1 mg/kg/injection *in vivo*

Acknowledgements

Chemistry

Peter Senter

Svetlana Doronina

Damon Meyer

Brian Mendelsohn

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Joe Francisco

Dana Chace

Jennifer Thompson